REMARKS

Claim 3 has been cancelled and its limitation ("superpotentiating") added to claim 1.

Formerly independent claim 2 is now a dependent claim that recites "separate" administration of the subject drugs. Claims 44 and 45, which originally depended on claim 2, have been cancelled. Claims 8 and 11 have been corrected.

An executed Terminal Disclaimer relating to U.S. Patent No. 6,713,470 and co-pending Application Serial No. 10/752,411 is submitted herewith. U.S. 6,713,470 and application 10/752,411 were both owned by the same entity when the inventions were made.

With respect to the objection to claim 3 and the term "superpotentiating," the application contains a description as what is meant (i.e., "... to enable the overall dose of opioid to be reduced or minimized, concurrent with improved analgesia..."; see page 2 lines 10-19). Thus, as amended the method recites a particular type of synergy that requires both reducing the opioid dosage while increasing the pain relief experience by the patient.

The term "*potentiating*" is well known in the art. The Latin prefix "*super*" is also well recognized, see below extract from http://www.answers.com/topic/super-prefix:

Super *pref.* [Latin, from super, over, above.]

1. Above; over; upon: *superimpose.*
2. Superior in size, quality, number, or degree: *superfine.*
3.
    a. Exceeding a norm: *supersaturate.*
    b. Excessive in degree or intensity: *supersubtle.*
    c. Containing a specified ingredient in an unusually high proportion: *superphosphate.*
4. More inclusive than a specified category: *superorder.*

Thus the term "*super*" in conjunction with "*potentiating*" is a term not only defined in the application as filed but could be easily be understood by a reader.

Claim 1 – 45 are rejected under 35 U.S.C 103(a) over WO 99/18967 and separately under 35 U.S.C 103(a) over Dourish et al.

It is acknowledged in the background section of the application that devazepide in combination with an opioid analgesic potentiates the analgesic effect of the overall dose of the opioid. In practice, a level of pain that is refractory-to-opioid is experienced despite a given dose of opioid thus devazepide is added to the opioid regimen, "*the expected outcome would result in the analgesia, or the "pain level", experienced by a patient generally remaining the same, whilst the dosage of opioid administered to the patient is reduced or analgesia improving with the same dose of opioid*" (page 2 lines 8 to 10). However, what has been unexpectedly observed in the present invention is that the use of devazepide can act not only to enable the overall dose of opioid to be reduced or minimised but that this is surprisingly "***concurrent with improved analgesia***, *i.e. an increase in the analgesia, or a lowering of "pain level", experienced by the patient. Indeed clinical studies have shown that the opioid dose may be reduced as much as 95% in some cases, in others as much as 75%. Thus, the administration of a combination of an opioid and devazepide does not just retain the 'pain level' experienced by a patient, but actually* ***improves*** *it, i.e. it is not just a case of opioid sparing or opioid potentiation, but the effect of the opioid is superpotentiated."* (page 2 line 13 to 20).

In summary, the expected or predictable outcomes for devazepide being added to an opioid dosing regimen are either:

1. The level of pain goes down and the dose of opioid stays the same (=potentiation) or;

2. The level of pain stays the same and the dose of opioid goes down (=potentiation)

However, what has been observed and would **not** be expected or predicted is that the level of pain goes down **accompanied** by the dose of opioid going down. This phenomenon has been termed '**super**potentiation' in the present application in order to differentiate it from the previously observed potentiation effects of devazepide.

Indeed, this phenomenon is substantiated in the clinical data of Table 2 and in particular reference to the patient referred to as "ap06/05", where it is shown that pain

relief was accompanied by a reduction of 54% in the tramadol dose. Further unpublished clinical trial data supports the observation of pain levels going down with accompanied reduction in opioid dose.

It is upon this hitherto unobserved and unexpected result that the present application is based i.e. the combination of CCK antagonist plus opiate analgesic does **more** than merely reduce the dose of opiate needed, but provides a qualitative improvement in pain relief not obtainable by simply increasing the dose of opiate. This phenomenon is not obvious from the prior art.

Panos et al is acknowledged as prior art and is discussed in the application as filed on page 1 line 12 through to page 2 line 7.

> *".....WO 99/18967 discloses the administration of devazepide in combination with an opioid analgesic so as to potentiate the analgesic effect of the overall dose of the opioid. In practice the expected outcome would result in the analgesia, or the "pain level", experienced by a patient generally remaining the same, whilst the dosage of opioid administered to the patient is reduced or analgesia improving with the same dose of opioid."*

Panos et al only discloses fixed pharmaceutical compositions of an opioid-potentiating amount of a CCK antagonist and an analgesic amount of an opioid with a biphasic carrier. Panos et al made no investigation into the effect of devazepide when the dose of opioid is altered / moderated. Thus, what Panos et al shows is option 2 of the predicted outcomes described above i.e. the level of pain stays the same and the dose of opioid goes down (=potentiation).

Panos et al. does not show or could be used to predict, that devazepide itself can act to enable the overall dose of opioid to be reduced or minimized, concurrent with improved analgesia, i.e. an increase in the analgesia, or a lowering of "pain level", experienced by the patient. Panos et al. does not show or give any direction that devazepide acts as a synergist or a superpotentiater allowing both a reduction in the opioid dose whilst increasing the effect of the analgesic i.e. the level of pain goes down **accompanied** by the dose of opioid going down.

As to the Dourish et al. publication, this discloses that "*devazepide may have therapeutic utility as an adjuvant to morphine analgesia allowing lower doses of the opiate to be used to relieve pain*" (last sentence of abstract). Devazepide was shown to enhance or potentiate the analgesic effects of morphine in squirrel monkeys in a dose-related manner with a bell-shaped response curves. On page 1160, column 2 under the paragraph beginning "Effect of devazepide on pain thresholds" and on line 8 of the abstract, it states that there was **no analgesic effect of devazepide *per se***. That is to say, devazepide has no intrinsic antinociceptive properties. Furthermore, the first three lines of text on page 1160, column 2 state that (following the determination of the antinociceptive effect of morphine in this model): "*A dose of 0.1 mg/kg of morphine was chosen as a sub-threshold dose to be used in the subsequent interaction experiments.*" There is no investigation into the effect of devazepide when the dose of opioid is altered / moderated it is only investigated at a sub-threshold level. Thus what the results of Dourish et al. show is option 1 of the predicted outcomes described above i.e. the level of pain goes down and the dose of opioid stays the same (= potentiation).

Dourish et al. does is counter-intuitive to devazepide acting as a superpotentiater allowing **both** a reduction in the opioid dose whilst increasing the effect of the analgesic i.e. the level of pain goes down **accompanied** by the dose of opioid going down.

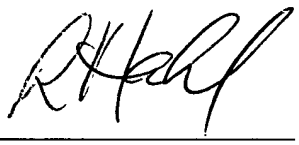
Applicant submits that the case is now in condition for allowance. Early notification of such action is solicited.

CONCLUSION

Applicant believes that no fee is required. However, the Commissioner is authorized to charge any fees deemed necessary and to make any refunds to Deposit Account 50-1710.

Applicants' undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should continue to be directed to our address given below.

Respectfully submitted,



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